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Effect of planar microelectrode geometry on neuron stimulation: Finite element modeling and experimental validation of the efficient electrode shape

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HIGHLIGHTS

- Stimulation efficiency of circular, spiral, and star perimeter electrodes with the same area was compared at the cellular level.
- Circular microelectrode requires less stimulus to activate a cell compared to the spiral and star perimeter shaped electrodes.
- The average current density and not the maximum current density of the electrode that determines its stimulation efficiency at the cellular level.
- Star electrodes with larger perimeter than circular electrodes did not result in higher neural stimulation efficiency at the cellular level.

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ABSTRACT

Background: Microelectrode arrays have been used successfully for neuronal stimulation both *in vivo* and *in vitro*. However, in most instances currents required to activate the neurons have been in unphysiological ranges resulting in neuronal damage and cell death. There is a need to develop electrodes which require less stimulation current for neuronal activation with physiologically relevant efficacy and frequencies.
New method: The objective of the present study was to examine and compare the stimulation efficiency of different electrode geometries at the resolution of a single neuron. We hypothesized that increasing the electrode perimeter will increase the maximum current density at the edges and enhance stimulation efficiency. To test this postulate, the neuronal stimulation efficacy of common circular electrodes (smallest perimeter) was compared with star (medium perimeter), and spiral (largest perimeter with internal boundaries) electrodes. We explored and compared using both a finite element model and *in vitro* stimulation of neurons isolated from *Lymnaea* central ganglia.
Results: Interestingly, both the computational model and the live neuronal stimulation experiments demonstrated that the common circular microelectrode requires less stimulus to activate a cell compared to the other two electrode shapes with the same surface area. Our data further revealed that circular electrodes exhibit the largest sealing resistance, stimulus transfer, and average current density among the three types of electrodes tested.
Comparison with existing methods: Average current density and not the maximum current density at the edges plays an important role in determining the electrode stimulation efficiency.
Conclusion: Circular shaped electrodes are more efficient in inducing a change in neuronal membrane potential.

1. Introduction

Biomedical engineering solutions are being sought to understand brain/neuronal function and these approaches range from multi-electrode arrays to implantable devices. One of the fundamental components of any such device is the efficacy of its

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recording and stimulation electrodes. Different approaches have been used to increase the efficacy of the electrodes used for neuronal stimulation. For instance, electrode geometry was found to affect neural stimulation efficiency by changing electrode impedance (Wei and Grill, 2009) and electric energy distribution in the tissue (Choi et al., 2004). Researchers have also studied different aspects of electrode geometry and its surrounding insulator layer that might increase the efficiency of deep brain stimulation (DBS) electrodes (Butson and McIntyre, 2006, 2006; Gimsa et al., 2006; Wei and Grill, 2005; Howell and Grill, 2014), external defibrillation electrodes (Krasteva and Papazov, 2002), and planar macroelectrodes (Wei and Grill, 2009).

DBS electrodes have an array of cylindrical electrode contacts which were studied by Wei and Grill (2005) to determine their stimulation efficiency. They concluded that a segmented electrode, when compared with a single solid electrode required lower stimulus strength to produce the same level of excitation in the surrounding tissue. Also, the impedance of these electrodes had an inverse relation with the number of segments. For instance, they reported that increasing the number of segments increases the efficiency of the electrode (Wei and Grill, 2005). Butson and McIntyre (2006) on the other hand investigated the effect of contact height and diameter of DBS electrodes on the volume of tissue activated (VTA). They found that an increase in electrode height caused a linear increase in the VTA, while an increase in the electrode diameter resulted in a logarithmic decrease in the VTA (Butson and McIntyre, 2006). Recently, Howell and Grill (2014) reported that electric potential distribution in the tissue is another factor besides electrode impedance that determines stimulation efficiency. Guo and DeWeerth (2009) studied the efficiency of protruded electrodes and reported that the protruded-well microelectrodes potentially result in better stimulation efficiency and focalization relative to planar electrodes by avoiding current leakage (Guo and DeWeerth, 2009). Lee et al. (2012) reported that pillar-shaped microelectrodes produce a more spherical conformity as compared to planar electrodes. However, an isolated pillar-shape electrode did not produce lower impedance as compared to a planar electrode with the same diameter (Lee et al., 2012).

Choi et al. studied the efficiency of electrodes used in a cochlear implant and demonstrated the impact of rectangular electrodes and insulators dimensions on focalization of stimulation. Specifically, they reported that smaller electrodes and smaller dielectric partitions produced more focalized electric energy in the auditory nerve and thus considered them to be the most efficient electrodes (Choi et al., 2004).

Similarly, Wei and Grill (2009) compared the efficiency of circular and serpentine planar macroelectrodes with different perimeters but with the same surface area. They studied the stimulation efficiency in stimulating a group of axons by comparing the activation function which is the second spatial derivative of extracellular potential that were produced by these electrodes. They found that serpentine electrodes with a larger perimeter were more efficient at stimulating axons farther away from the electrode. The electrochemical impedance spectroscopy (EIS) of different electrodes did not however show significant difference between the impedance of different geometries at several frequencies (Wei and Grill, 2009). Similarly, Sekirnjak et al. (2006) investigated the effects of electrode size on the efficiency of stimulation and studied the feasibility of using small electrodes for stimulating retinal neurons. Their experimental data showed that smaller electrodes required less stimulation current and charge but more current and charge density to elicit spike in a group of ganglion cells (Sekirnjak et al., 2006).

Despite progress made by the above studies, the effects of other geometry factors such as internal boundaries and external perimeters on current density distributions and stimulation efficiency have not been investigated, especially at the level of single neurons. To this end, we examined the stimulation efficiency of three different geometries of planar electrodes using identified and well-characterized *Lymnaea* neurons. The choice of planar microelectrodes in this study was based on their wide application in fundamental research areas via commercially available microelectrode arrays (MEA). Specifically, common two-dimensional circular microelectrodes were compared to spiral-shaped electrodes, which represent electrodes with internal boundaries, and star-shaped perimeter electrodes, representative of larger perimeters than circular electrodes. In addition, the stimulation efficiency of a microelectrode was studied via its effect on an individual cell rather than a highly complex and intricate neuronal tissue. This approach eliminated several variables thereby providing direct measurements in the absence of other confounding factors present in the extracellular milieu. To test the stimulation efficiency, we first calculated the current density and membrane depolarization factors by using a finite element model (FEM). Our theoretical modeling predictions were then verified experimentally by using sharp electrode intracellular recordings of membrane potential changes in single *Lymnaea* neurons cultured on top of individual microelectrodes.

2. Methods

2.1. FEM

To simulate the neuron electrode interface via FEM, the electric current mode of COMSOL4.3b (COMSOL Inc., USA), a FEM software package, was used to model the interface in three dimensions. A transient FEM was developed to simulate a passive neuronal response to a subthreshold stimulus. The electric current mode of COMSOL software solves the charge conservation equation, (1) for the electric potential, V, as the dependent variable. In this case the electric potential satisfies Laplace's equation, (3). Three electrode geometries, circular, spiral, and star perimeter, were modelled to study the current density, transmembrane potential, and intracellular electric potential produced by each electrode shape.

$$\nabla \cdot J + \frac{\partial \rho}{\partial t} = 0 \quad (1)$$

where J is given by:

$$J = \sigma E = -\sigma \nabla V \quad (2)$$

$$\nabla \cdot J + \frac{\partial \rho}{\partial t} = \nabla^2 V = 0 \quad (3)$$

The model includes six domains; substrate, electric double layer (EDL), sealing gap, membrane, intracellular, and extracellular. A schematic view of the model is illustrated in Fig. 1.

The gap between the cell and electrode, i.e. the sealing gap, as reported in literature for the snail neuron on poly-L-lysine is 51 ± 2 nm thick (Schoen and Fromherz, 2008; Zeck and Fromherz, 2003). In order to have a realistic model of an individual cell a membrane with a thickness of 8 nm (Huang et al., 2004) has also been implemented in the model. Since the electric field in the metal electrode is zero and the metal surface is an equipotential surface, the electrode was modelled by its surface rather than its whole volume. The glass substrate with an actual thickness of 1 mm was modelled as a cylinder with a height of 10 μm. The extracellular domain was modelled as a 120 μm diameter hemisphere. Doubling the height of the substrate or diameter of the extracellular volume did not result in significant changes in the values of electric potential obtained as the solution of the FEM. The neuron was modelled as a paraboloid with a radius of 30 μm and height of 20 μm, height = 0.7 * radius (Buitenweg et al., 2003). The thicknesses of the sealing gap, cell